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Extreme obesity in female rats following prepuberal induction of lithium–pilocarpine seizures and a single injection of acepromazine

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Abstract

Seizures were induced in female Wistar albino rats at either 35 or 55 days of age with a single systemic injection of lithium (3 mEq/kg) and pilocarpine (30 mg/kg); the rats were then treated with the atypical neuroleptic acepromazine (25 mg/kg). These rats manifested progressive weight gain for the rest of their lives. The effect was conspicuous by casual observation 6 weeks after treatment and occurred primarily in those rats that later developed spontaneous seizures. After 1 year, the rats were obese (>1000 g). Such weight gains, associated with almost three times the serum triglyceride levels, were not observed in male rats and have not been observed in hundreds of female rats that received this treatment as adults. Single postseizure injections of ketamine rather than acepromazine did not produce this obesity; the weights of these rats were similar to those of normal littermates. These results indicate that a *single* injection of a neuroleptic during limbic seizures before puberty can produce neuronal alterations that contribute to a lifetime of obesity.
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1. Introduction

In rats, hyperphagia and obesity can be induced by electrolytic lesions within the ventromedial hypothalamus or within the posterordorsal part of the medial amygdaloid nucleus [1]. The weight gain is more obvious in female rats than in male rats and has been attributed in part to the sex differences in the circulating efficacy of leptin [2,3]. Recently, Loscher et al. [4] found that twice-daily electrical kindling of the basolateral nucleus of the amygdala for up to 280 stimulations was associated with average weight gains of about 100 g compared with a group that received conventional kindling (20 stimulations) or with controls. The effect emerged about 3 weeks after the initiation of treatment and approached asymptote at about 30 weeks.

Another method [5] for inducing seizures involves a single systemic injection of either lithium (3 mEq/kg) and pilocarpine (30 mg/kg) or a larger dosage [6] of pilocarpine (about 400 mg/kg). The resultant status epilepticus produces significant mortality in adult rats (>70 days of age) unless they are injected with ketamine followed by benzodiazepines and barbiturates [7,8]. The age dependence of both survival following single lithium/pilocarpine injections and the distribution of neuropathology has been shown by Druga et al. [9]. Repeated low-dose treatment of rats with pilocarpine results in low mortality but high proportions of rats developing epilepsy [10].

In both male and female rats, the induction of epilepsy by this method leads to emergence of overt spontaneous seizures (characterized by rearing, rapid forelimb clonus, and falling) after a quiet period of between 10 and 50 days [11]. During the silent phase progressive metabolic changes underlying chronic reorganization of brain

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circuits occur in both the immature (21-day) and mature rat [12]. Behavioral sampling of these daily seizures suggests they occur at least once per day [13]. These overt behaviors are associated with long-lasting alterations in calcium homeostatic mechanisms that persist up to a year after the induction of epileptogenesis [14].

Because we have focused on the long-term behavioral consequences following the induction of epileptic seizures and the different patterns of neuronal damage produced by various postseizure treatments, we [15] have employed a variety of atypical compounds that promote survival and produce specific patterns of damage within the "neuromatrix." One of these drugs was the atypical neuroleptic acepromazine. For example, we found that maternal behavior (several months later) in rats could be abolished if acepromazine was given after induction of lithium/pilocarpine seizures [16]. A single postseizure injection of ketamine (100 mg/kg) produced comparable overall neuronal damage, but the pattern of damage within specific subcortical telencephalic and diencephalic nuclei was different from that in brains of rats that received the acepromazine. The ketamine-injected seized rats exhibited normal maternal behaviors.

While examining the potential age range in which seizures could be induced and maternal behavior would not be abolished, the first author observed the progressive adult weight gains in rats seized during prepubertal development. Casual observation showed the more obvious weight gains when seizures were induced around 35 and 55 days of age. The present experiments were designed to explore this phenomenon quantitatively. We selected offspring from both culled and unculled litters to discern if this type of earlier experience might obviously attenuate the weight gain.

2. Method

2.1. General procedure

There were five experiments over a 2-year period. They involved 127 female rats and 52 male rats. The Wistar albino breeders (the parents) were obtained at 60 days of age from Charles River. After habituating to standard wire cages in temperature (20 °C)-controlled rooms with a 12-hour light:dark cycle, the rats were bred. About 5 days before delivery, the mothers were housed in standard plastic cages with corncob bedding. Litters were weaned at 21 days of age. In all experiments Purina rat chow was available ad libitum. All analyses involved SPSS software on a VAX 4000 computer. The numbers of rats selected to be studied per experiment were calculated by the expected effect size (omega-squared estimate) of the treatment and according to the guidelines for minimal usage of animals from the Canadian Council for Animal Care.

2.2. Comparison of weights following injections at either 35 or 55 days of age

One female rat from each of 12 unculled litters (13–16 pups per litter) was injected subcutaneously with lithium chloride (3 mEq/kg, 3 mEq/cc) and, 4 hours later, with 30 mg/kg pilocarpine (30 mg/cc) in water on either Postnatal Day 35 ($n = 12$) or 55 ($n = 12$). Immediately after onset of the easily identifiable overt seizures (rearing, rapid forelimb clonus, and falling), the rats were injected subcutaneously with 25 mg/kg acepromazine (Atravert, Ayerst Labs, Montreal, Canada). Another two female rats from each of the 12 litters were injected with either only lithium ($n = 12$) or only acepromazine ($n = 12$); 6 of the rats were given the lithium only or acepromazine only on Postnatal Day 35; the others were given the treatment on Postnatal Day 55. Another 11 rats (one litter did not have any remaining females), 6 on Postnatal Day 35 and 5 on Postnatal Day 55, were simply handled (total $n = 59$). They remained in group housing (3 or 4/cage) until they were weighed at 100 days of age. Because there were no statistically significant differences between the various reference rats (lithium- or acepromazine-injected only, or handled controls), these groups were combined and defined as the control group. Two-way analysis of variance for the body weights as a function of when the rats were seized (35 vs 55 days of age) and treatment (seized plus acepromazine vs control) was completed.

2.3. Comparison of acepromazine and chlorpromazine

Two female rats from each of eight litters ($n = 16$) that had been culled to eight pups at 21 days of age were injected subcutaneously at 35 days of age with the lithium/pilocarpine solutions. Immediately after seizure onset, the rats were injected with either acepromazine (25 mg/kg, $n = 8$) or chlorpromazine (CPZ, 10 mg/kg, $n = 8$). CPZ was selected as a drug for comparison because it affects both D1 and D2 (dopamine) receptors, and this system has been implicated for the development of pseudocyesis and adiposity [17].

In a parallel study, eight rats (one from each of the same litters) were injected with lithium/pilocarpine but did not display the overt seizures, a phenomenon that occurs more frequently (for unclear reasons) in female rats. Only two rats survived and were considered a reference group to discern if they differed conspicuously from normal rats. Another eight rats (one from each litter) served as normal controls (total $n = 26$). The rats were housed singly in plastic cages containing corncob bedding and were weighed every second day after the seizure induction for 4 weeks and again after 28 weeks. One two-way analysis of variance with one within-subject level (first 4 weeks) and one between-subject level (treatments) and a single one-way analysis of variance for body weights taken 28 weeks later were completed.

2.4. Long-term obesity, blood (serum) measures, and tissue weights: comparison with postseizure ketamine injections

Three female rats from each of five different ($n = 15$) unculled litters were injected at 55 days of age with lithium/pilocarpine. Ten seized; after seizure onset, five were injected with acepromazine (25 mg/kg) and five were injected with ketamine (100 mg/kg). The five rats (one from each litter) that did not seize served as reference controls; another four rats from the same litters were simply handled at that time (total $n = 19$). Ketamine was selected because: (1) rats seized with lithium/pilocarpine and then injected with this noncompetitive NMDA antagonist have not shown the behavioral deficits exhibited by rats seized by this method but given acepromazine [18,19], and (2) rats treated with ketamine after seizure induction do not appear to develop the overt seizures even after delays of 1 year [20]. They were maintained for the rest of their lives in plastic cages (either two or four per cage). Body weights were recorded after 32, 42, 52, and 62 weeks had elapsed. A three-way analysis of variance with one within-subject level (four periods) and two between-subject levels (postseizure treatments and cage density) was completed.

Eleven of these rats (four control, four seized and given acepromazine, and three seized and given ketamine) were decapitated at 62 weeks of age. Serum from the trunk blood was analyzed automatically at a local medical unit for AST (aspartate aminotransferase), ALP (alkaline phosphatase), ALT (alanine aminotransferase), LDH (lactate dehydrogenase), sodium, chloride, potassium, phosphorus, calcium, albumin, cholesterol, triglycerides, glucose, creatinine, uric acid, and blood urea nitrogen. Wet weights were measured to the nearest 0.1 mg for thymus, thyroid, spleen, pancreas, adrenal glands, ovaries, hypophyses, and brain.

2.5. Increased availability of food

The manner of food availability was modified for three of the fattest rats seized at 55 days of age and injected with acepromazine. By age 9 months their weights had asymptoted between 960 and 980 g. They were given rat chow on the bottom (corncob bedding) of their cages as well as through the hoppers so constant nibbling would be possible. The rats were weighed each week for an additional 4 weeks (total $N = 3$).

2.6. Spontaneous seizures and weight gain

A total of 10 rats from five unculled litters (two per litter) were seized between 53 and 55 days of age with lithium and pilocarpine and then treated with acepromazine. Another 10 littermates served as controls. The rats were housed in pairs (one seized, one not seized) within standard plastic shoebox cages containing corncob bedding. There was no significant difference between the groups with respect to baseline (preseized) body weights. Body weights were recorded 2, 4, 6, 9, 11, and 13 weeks after the treatment. Five of the rats were observed to have at least one spontaneous seizure defined as rearing, rapid forelimb clonus, and a subsequent (about 20 seconds later) hyperactivity (''fearfulness'') during either weighing or daily surveillance of the rats. Because we have found that disturbance of the cage can precipitate spontaneous seizures [11,13], the rats were transported in their home cages to another room in the facility once per week for 2 hours. The other five seized rats did not exhibit any obvious clinical manifestations during the observation periods. To maintain symmetry in analyses, only 5 of the 10 control rats that had been paired in permanent housing with a seized rat were included in this analysis (total $N = 15$).

2.7. Male rats and weight gains

To discern if the weight gains subsequent to seizures and treatment with acepromazine before puberty occurred in male rats, 26 male littermates from the 13 litters in Section 2.2 (the additional litter contained only two females) were injected with lithium/pilocarpine followed by acepromazine at 35 days of age. A second group of 26 male littermates served as nonseized controls (total $n = 52$). The rats were housed in groups of three (at least one seized and one control rat per cage) within standard wire cages. Body weight was recorded at 120 days of age.

3. Results

3.1. Comparison of ages at injection and treatments

The results of the two-way analysis of variance showed that the group in which seizures were induced and then treated with acepromazine displayed significantly [$F(1, 54) = 15.22$, $P < 0.001$] heavier body weights ($M = 322$ g, SD = 37 g) compared with the other groups ($M = 284$ g, SD = 35 g) 7 weeks after the treatment (100 days of age). Within 4 weeks (130 days), the seized rats given acepromazine were still significantly [$F(1, 54) = 24.95$, $P < 0.001$] heavier ($M = 408$ g, SD = 94 g) compared with the other groups ($M = 350$ g, SD = 91 g). These two main effects explained 22 and 32% of the variance in the body weights, respectively. Neither the main effect for differences between ages at the time of injection [$Fs(1, 53) < 1.00$, $P > 0.05$] nor the interactions [$Fs(2, 53) < 1.00$, $P > 0.05$] between age of injection and postseizure treatments were statistically significant.

3.2. Comparison of neuroleptics

The statistically significant differences [$F(3,16) = 6.69$, $P < 0.01$; $\eta^2 = 0.50$] between the four conditions for weights 28 weeks after the single treatments on Postnatal Day 35 were shown by post hoc analysis to be due to the significantly heavier body weights displayed by the rats that received the acepromazine after seizure induction ($M = 461$, SD = 26) compared with either the normal rats ($M = 337$, SD = 15) or those that received lithium/pilocarpine and did not seize ($M = 341$, SD = 44). The group that received chlorpromazine ($M = 424$, SD = 34) occupied an intermediate position. Six of the rats that displayed seizures and then received acepromazine and three of rats that seized and then received chlorpromazine displayed spontaneous seizures that began about 2 weeks after the initial induction. The two rats that did not seize following lithium/pilocarpine injection did not display spontaneous seizures. There were no significant differences in body weights between the groups during the first 4 weeks after treatment.

3.3. Long-term effects: blood measures and wet tissue weights

By far the most impressive effect occurred with advanced aging. At 62 weeks after treatment, rats that had seized and had been given the single injection of acepromazine were more than twice as heavy ($M = 777$ g, SD = 136 g) as their littermates (with whom they had been housed for a year) who had been either (1) only handled ($M = 385$ g, SD = 7 g), (2) injected with lithium/pilocarpine but not seized ($M = 380$ g, SD = 34 g), or (3) seized but given a single injection of ketamine ($M = 446$ g, SD = 79 g). The rats that seized and received the acepromazine all exhibited spontaneous seizures. The ketamine-treated rats were never observed to display this behavior. None of the five rats that were injected with lithium/pilocarpine but did not seize were observed to display spontaneous seizures over their lifetimes.

There was no overlap in the body weights between the rats that seized and received acepromazine and rats from any of the other three groups. An example of a rat that received acepromazine after seizure induction and a littermate that received ketamine after seizure induction is shown in Fig. 1. Post hoc analysis of the statistically significant differences between postseizure treatments [$F(3,9) = 14.72$, $P < .001$; $\eta^2 = .83$] indicated that the seized acepromazine rats were significantly heavier than the other three groups, which did not differ significantly from each other. There were no significant differences in body weights between the two densities in which the rats lived for more than a year [$F(1,9) = 0.44$, $P > 0.05$] and no statistically significant interaction between density and group [$F(3,9) < 1.00$, $P > 0.05$]. The statistically significant interaction between time and condition [$F(9,27) = 6.37$, $P < 0.001$; partial $\eta^2 = 0.68$] was due in large part, according to post hoc t tests, to the greater increase in body weights over time for acepromazine-treated, seized rats compared with any of the other three groups.

The blood measures and organ weights that displayed statistically significant group differences as well

Fig. 1. Photograph of an obese 1-year-old female rat that had been seized around 55 days with lithium and pilocarpine and then given a single injection of acepromazine (25 mg/kg). For comparison, a female littermate that had been seized but given ketamine (100 mg/kg) is shown. The size of the latter was typical of a normal female rat for this age.

as selected measures of immediate relevance (but not statistically significant) to the correlates of obesity are listed in Table 1. Those not listed also showed no statistically significant group differences. The rats that had been seized and given acepromazine (fat rats) had significantly [$F(2,8) = 11.87$, $P < 0.001$; 72% of variance explained] higher triglyceride (but not cholesterol) but lower chloride [$F(2,8) = 5.64$, $P < 0.02$] concentrations compared with the control group or the group that had been seized but given ketamine. The serum of the rats that had been seized and given acepromazine was concentrated white rather than the usual clear or slight pink color. These fat rats also showed significantly heavier thymuses and adrenal glands than the other two groups, whose weights for these organs did not differ significantly from each other.

There were also no statistically significant group differences for the weight of the brain ($M = 2.07$ g, SD = 0.09 g), pituitaries ($M = 15$ mg, SD = 2 mg), pancreases ($M = 901$ mg, SD = 261), ovaries ($M = 115$ mg, SD = 32 mg), or thyroids ($M = 27$ mg, SD = 6 mg). The grand means and SD for the other blood measures that did not display group differences were AST (U/L) 159 (43), Na (mEq/L) 150.0 (2.9), P (mg/dL) 2.62 (0.40), LDH (U/L) 750 (284), uric acid (mg/dL) 68.9 (28.2—one fat rat had a value of 140), blood urea nitrogen (mg/dL) 8.5 (1.0), ALP (U/L) 148 (113), creatinine (mg/dL) 36.5 (9.2), Ca (mg/dL) 3.2 (0.1), and ALT (U/L) 49.4 (23.6).

3.4. Increasing food availability

All three of the obese rats whose weights had asymptoted around 980 g gained additional weight quickly when the food was also available ad libitum on the cage floor. Within 2 weeks the weights of all of these rats exceeded 1000 g and within 4 weeks, approached 1080 g. These rats displayed spontaneous seizures almost daily when new food was added to the floor of the cages. They were restricted overtly to dorsoflexion of the head and paddling for the forelimbs.

3.5. Spontaneous seizures and weight gain

The means and SEM for body weights 2, 4, 6, 9, 11, and 13 weeks after the treatment for groups of rats that were seized and either did ($n = 5$) or did not ($n = 5$) display spontaneous seizures, or served as littermate controls ($n = 5$) are shown in Fig. 2. The F values (all df = 2,12), P values, and amount of explained variance (omega-squared estimates) for the group differences for these weeks were 2.67 (n.s., 30%), 3.75 (n.s., 38%), 5.95 ($P < 0.01$; 50%), 5.95 ($P < 0.01$; 50%), 7.22 ($P < 0.01$; 54%), 9.79, ($P < 0.001$; 62%), 14.24 ($P < 0.001$; 72%), and 43.47, ($P < 0.001$; 88%), respectively. Post hoc analyses (Tukey's $P < 0.05$) showed that the major source of the statistically significant differences was due to the significantly heavier weights for the rats that were observed to display spontaneous seizures during the weeks that followed the induction compared with the rats that were seized but who were not observed to display these seizures. They did not differ significantly from the littermate nonseized controls.

3.6. Male rats

The body weights ($M = 462$ g, SD = 62 g) of 26 4-month-old male rats from the same litters as the females who gained weight and that were seized by this method around 35 days of age did not differ significantly [$F(1,50) < 1.00$, $P > 0.05$] from those of their 26 littermate controls ($M = 465$ g, SD = 45 g).

4. Discussion

The results of these experiments showed that female rats seized with lithium and pilocarpine on 35 or 55 days of age and then injected with 25 mg/kg acepromazine

Table 1
Means and SD for body weights, selected blood (serum) measures, and selected wet organ weights of 62-week female littermates that had been seized at 55 days of age and given either acepromazine or ketamine, or not seized (but handled)

Variable	Controls		Seized + acepromazine		Seized + ketamine	
	M	SD	*M*	SD	*M*	SD
Body weight (g)	375[a]	45	776[b]	150	431[a]	51
Albumin	48.7	4.1	40.2	3.5	42.7	7.6
Triglycerides	3.0[a]	1.1	8.2[b]	2.5	2.6[a]	0.8
Cholesterol	2.9	0.6	5.6	2.4	3.1	0.3
Glucose	7.9	0.5	8.4	1.6	7.5	0.5
K	7.3	0.8	8.1	0.5	6.9	0.3
Cl	103.3[a]	1.5	100.0[b]	1.1	103.7[a]	0.6
Thymus (mg)	164[a]	31	275[b]	56	82[a]	43
Spleen (mg)	870	41	1229	253	1042	252
Adrenals (mg)	80[a]	5	113[b]	26	62[a]	3

a versus b = $P < 0.05$.

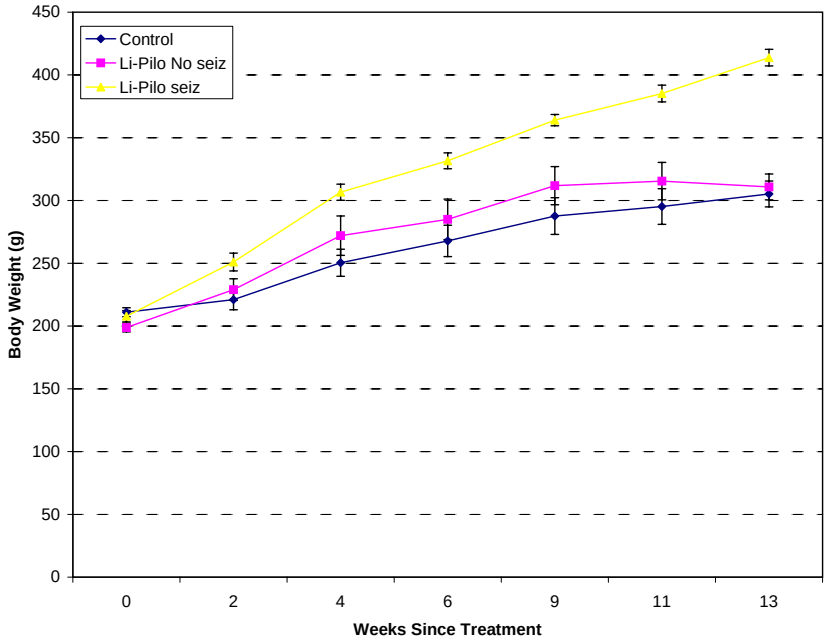

Fig. 2. Means and SEM for body weights over time (in weeks) for rats that were seized with lithium and pilocarpine and treated with acepromazine between 53 and 55 days of age and who either did or did not develop spontaneous seizures during subsequent weeks. Littermate control weights are also shown.

shortly after the onset of overt seizures (about 30 minutes) displayed an insidious increase in body weight that continued throughout their lives. The obesity was not associated with premature deaths. For all experiments only one (seized) rat, within 2 months of the production of the seizures, died suddenly and unexpectedly. The obesity was not observed in male littermate rats that were seized at similar ages and treated with acepromazine.

Within 7 to 9 weeks after this single treatment, the female rats were more than 100 g heavier than age-matched controls. The single treatment explained about 75% of the variance in the body weights. The amount of weight gain was similar to the consequences of extended kindling reported by Loscher et al. [4]. Both effects emerged after about 4 weeks and had appeared to asymptote by Week 28. However as aging progressed in our study, and 32, 42, and 52 weeks had elapsed since the treatment, the rats seized by lithium and pilocarpine and given acepromazine became extremely obese.

Their body weights, even if housed in groups of two or four, ranged between 600 and 980 g. The apparent "limit" of about 980 g noted in several rats was likely an artifact of the manner in which they obtained food. When a small sample of these fat rats were given the same rat chow on the floor (corncob bedding) of their cages, they all gained an excess of 1000 g. These rats would begin consuming the food as soon as it was introduced.

All of the old and very fat rats were observed to have displayed the occasional spontaneous forelimb clonus (motor seizures) during their lifetimes while the experimenters were in the housing rooms for daily monitoring. These seizures were almost always followed, about 20 seconds later, by exaggerated hyperresponsiveness and "fear" behaviors reminiscent of classic amygdaloid electrical activity. Littermates that had been seized and had received ketamine remained lean. Their body weights were not significantly different from those of age-matched controls. The ketamine-treated rats also never displayed spontaneous seizures in this study or our other studies [18–20] or those reported by Hort et al. [8].

In the experiment where the occurrences of the spontaneous seizures were more closely monitored, only the rats in which spontaneous seizures were observed to occur during the weeks that followed the seizure induction exhibited the significant gains in weight. We cannot eliminate the possibility that the seized rats that did not display overt seizures and that did not differ in weight from nonseized controls may have displayed seizures during periods when they were not observed.

"Kindling" is very likely to occur during the "silent period" that precedes the overt display of spontaneous seizures in rats in which epilepsy was induced by either lithium/pilocarpine or 380 mg/kg pilocarpine [8,20]. We suggest that the maintenance of this kindling in rats may have been encouraged by the neuronal "reorganization" that was created by the consequences of the combination of the damage produced by the seizures and their interactions during the first few hours with the effects mediated by acepromazine. Support for this

explanation is the observation by Dube et al. [12] that progressive metabolic changes underlie the chronic reorganization of brain circuits in both the immature and mature rat brain. That long-term changes in calcium metabolism may have contributed to these changes has been suggested by Raza et al. [14].

Adult rats in which the seizures were induced did not gain excessive weight as they matured and actually weighed less than age-matched controls [15,20]. Brain damage, usually displayed as neuronal dropout and cystic lesions, occurred in various degrees within dozens of structures throughout the diencephalon and telencephalon, including the amygdala [18,19,21–24]. The right side of the brain was slightly more affected than the left, and the numbers of spontaneous seizures per month during the year following the "quiet period" were correlated positively with the proportions of neuronal dropout within the right temporal cortices [11].

Adult females that were treated with acepromazine following the lithium/pilocarpine induction of seizures and then impregnated showed complete abolishment of maternal behavior including the display of infanticide [16]. Rats that received ketamine (100 mg/kg) instead of acepromazine were normal mothers despite similar total neuronal damage. Rats injected with ketamine after seizure induction never developed spontaneous (overt) seizures. It may be relevant that one of the most significant differences in the mosaic of neuronal dropout within the brain after seizure induction is the near-total loss of neurons within the hippocampal–amygdaloid transition area (particularly in the right hemisphere) for rats treated with ketamine but not with acepromazine.

Loscher et al. [4] showed that extended kindling within the basolateral amygdala produced marked weight gains in adult female rats. The simplest explanation for the absence of weight gain in adult rats treated with acepromazine after seizure induction but the conspicuous obesity in rats seized between 35 and 55 days of age and treated with acepromazine (but not ketamine) would require an age-dependent sensitivity of this area to the synergistic effects of the seizure-induced damage and acepromazine. A similar but not as intense effect should be evident for the (dopamine) D1/D2 receptor antagonist chlorpromazine. Cytometric density within this area for postseized, ketamine-injected rats should be similar to that of controls.

The results of this study emphasize the importance of the age of the rat at the time of the "neuroelectrical stress" and the pharmacological treatment. We suggest that leptin, a product of the obese (*ob*) gene [2], may have been permanently altered by the occurrence of this neuroelectrical–pharmacological synergism at a single time point in ontogeny. Leptin has shown sex differences in circulating efficacy [2,3]. It may be relevant that in other studies (St-Pierre, unpublished data) 25-day-old female rats that received this treatment developed (within about 2 weeks) pseudopregnancy, the magnitude of which was sufficient to be misinterpreted by animal technicians as approximately Postconception Day 19 or 20. Because the medial amygdala is involved with the neurochemical processes that invoke both pseudopregnancy [17] and obesity [14] in the female rat, the organization or electrical patterns within this structure may be involved with both processes.

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